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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,333	02/10/2004	Michael Moshman	077350.0136	1725

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BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

EXAMINER	
MERCIER, MELISSA S	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
08/26/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DLNYDOCKET@BAKERBOTTS.COM

Office Action Summary	Application No.	Applicant(s)	
	10/776,333	MOSHMAN ET AL.	
	Examiner	Art Unit	
	MELISSA MERCIER	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-2, 4-36* is/are pending in the application.

5a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-2, 4-17, 20-36* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 12, 2011 has been entered.

Information Disclosure Statement

Receipt of the Information Disclosure Statement filed on July 20, 2011 and August 12, 2011 is acknowledged. A signed copy of the 1149 filed on August 12, 2011 is attached, however, the document filed on July 20, 2011 did not include a 1449 form, therefore, it is an improper IDS. Applicant is requested to file a PTO-1449 with the references cited in order to have them considered by the Examiner.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-9, 12, 14-17, and 20-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum et al. (US Patent 6,387,917) in view of Grebow et al. (US Patent 5,026,825).

Illum discloses a methane sulphonate salt of morphine and compositions thereof having medicinal uses, particularly for the treatment of pain and adapted for nasal delivery (abstract). Illum discloses the methane sulfonate salt of morphine is commonly termed mesylate (column 2, lines 31-35). The preferred composition comprises aqueous solutions in which the methane sulphonate salt is combined with chitosan to provide an increased absorption of the drug (column 2, lines 61-68). The morphine methane sulphonate liquid formulation will comprise 0.1mg/mL to about 600mg/mL morphine content (column 4, lines 20-24). The formulation may also be incorporate into formulations suitable for oral, buccal, rectal, or vaginal administration (column 4, lines 39-42). Illum's Examples 2-3 discloses a solution for intranasal administration comprising 8g morphine base (monohydrate), to which 2M methane sulphonic acid solution is stirred in, and 25mL of chitosan (column 5, line 33 through column 6, line 21). It is noted in claim 9, that Applicant has identified methane sulfonic acid as an antioxidant. The prior art teaches mixing morphine base monohydrate with methane sulphonic acid in which no additional method steps are performed, (i.e. heating, precipitation), then adding the chitosan solution. Therefore, Applicants is directed to their own specification on page 10-11, in which Applicant has used the same method steps as Illum, and would necessarily result in the conversation of the base

monohydrate to the methane sulphonate salt of morphine. Example 2 additionally discloses a weight ratio of morphine (150mg/ml) to chitosan (5mg/ml) is 10:1, thereby meeting the claim limitations. As discussed above, the morphine can also be present in the amount of 0.1mg/ml to 600mg/ml; therefore, the skilled artisan would be able to determine the optimal therapeutic benefit by optimizing the morphine to chitosan ratio based on the teachings of Illum.

The pH of the formulation is adjusted to a range of about 4-7 by adding additional methane sulfonic acid solution or an alkali (column 3, lines 36-40).

Illum further discloses the formulation can also contain other ingredients such as buffer systems, pH modifiers, anti-oxidants, stabilizing agents, anti-microbial agents, chelating agents, viscosity-enhancing agents, or other agents generally used in pharmaceutical formulations (column 4, lines 25-29).

While Illum discloses the use of antimicrobial agents, Illum does not disclose the use of benzalkonium chloride, disodium EDTA, sodium benzoate, and combinations thereof.

Grebow discloses an intranasal formulation comprising antimicrobial agents including benzalkonium chloride and disodium EDTA (Examples). They are present in the amount of 0.001-2.0% (w/v) (column 11, lines 55-63).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the specific antimicrobial agents of Grebow into the formulation of Illum since Grebow discloses they are suitable for use in nasal inhalant formulations.

Illum does not disclose the molecule to molecule ratio of morphine to chitosan recited in the instant claims. Illum does however disclose the same weight ratios recited in the specification on which would result in the claimed linear absorption rates upon administration. , therefore, it is the position of the Examiner that since Illum discloses the same morphine and the same chitosan in the same weight ratios as recited as able to silicate the desired release, it would also meet the limitations of the molecule to molecule ratio, absent a showing of evidence to the contrary.

Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various transmucosally compositions having various amounts of the active agent and chitosan polymers is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a showing of criticality. See In re Russell, 439 F.2d 1228 169 USPQ 426(CCPA 1971).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Applicants note that morphine formulations have encountered stability problems and cite one specific FDA recall.**

It is noted in the recall notice by the Examiner obtained from the FDA website; the product was recalled due to a failure in stability testing. However, there is no evidence on in the notice, nor has there been any evidence submitted by Applicant that

this failure in stability is a result of an antimicrobial agent. There are numerous conditions that could have resulted in this failure, not addressed by Applicant.

***The presence of Δ-aminolevulinic in Grebow is relevant because it is added to the formulations to prevent degradation of the active agent and Illum does not require such an agent.**

Applicant has conceded that Illum does not disclose his product has stability issues regarding degradation. Applicant has also not provided any evidence directly linking the use of different antimicrobial agents result in the degradation of the morphine.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Illum et al. (US Patent 6,387,917) in view of Grebow et al. (US Patent 5,026,825) and further in view of Tulin-Silver et al. (US 5,508,282).

The teaching of Illum and Grebow are discussed above and applied in the same manner.

Illum discloses the use of antioxidant; however, Illum does not disclose the specific use of ascorbic acid or sodium ascorbate in the amount of 40-70mg/mL.

Tulin discloses compositions and methods for the treatment of rhinosinusitus comprising ascorbic acid in a nasal spray (abstract) in the amount of 15-300mg/ml (Table I).

It would have been obvious to one of ordinary skill to have incorporated the ascorbic acid of Tulin in the formulation of Illum since Tulin discloses it's useful for

shortening the symptoms and duration of rhinitis or rhinosinusitis without side effects (column 3, lines 5-8).

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Illum et al. (US Patent 6,387,917) in view of Grebow et al., (US Patent 5,026,825) and further in view of Santus et al.(US Patent 6,333,044).

The combination of Illum and Grebow are discussed above and applied in the same manner.

Illum and Grebow do not disclose the use of sodium benzoate as an antimicrobial agent.

Santus discloses nasal spray formulations comprising antimicrobial agents. Sodium benzoate is disclosed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the specific antimicrobial agents of Santus into the formulation of Illum and Grebow because it is disclosed as suitable for use in nasal inhalant formulations.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues:

***Applicant need not submit any evidence comparing the stability of the products with and without the selected antimicrobial agents because the Examiner has not shown that the composition of Illum is stable.**

It is the position of the Examiner that since Illum does not disclose his formulation to be unstable, there is nothing of record to show that it is unstable, then the formulation is presumed to be stable. Applicant is invited to provide any contradictory evidence.

Conclusion

All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA MERCIER whose telephone number is (571)272-9039. The examiner can normally be reached on 8:00am-4:30pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
August 23, 2011